Comparison of Estimated PCB-153 Concentrations in Human Milk Using Various Pharmacokinetic Models

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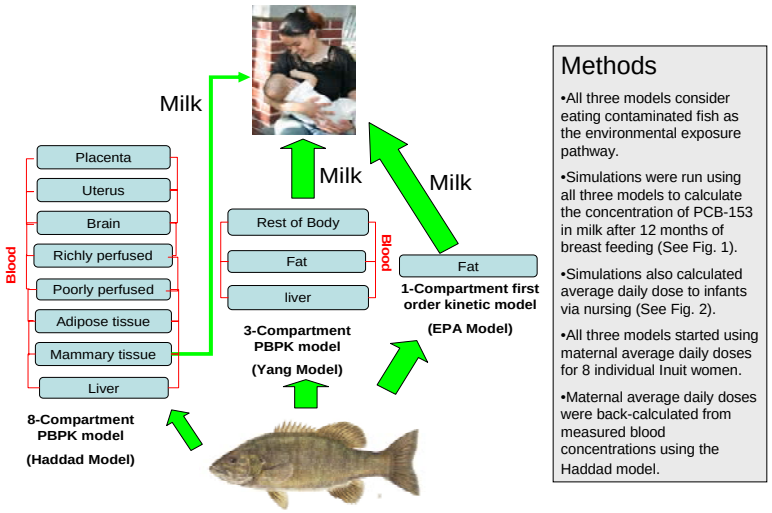
Introduction

Background: Lipophilic environmental contaminants, such as polychlorinated biphenyls (PCBs) can concentrate in human milk. Risk to infants from consuming the milk of mothers exposed to PCBs has not routinely been quantitatively addressed in environmental risk assessments. Current environmental risk assessment guidance does not account for the significant bioconcentration in the adipose of an expectant mother that will be mobilized and incorporated into her milk. To adequately protect nursing infants, an especially vulnerable population, the breastfeeding pathway should be considered when assessing risk at sites where lipophilic contaminants are present. Obtaining human milk samples to measure contaminant concentrations is not practical in most cases, so it is desirable to have a method to estimate milk concentrations based on a lifetime average daily dose to the mother. Multiple models have been developed to produce these estimates.

Objectives: Our 3-fold objective was to 1- Evaluate the precision of disparate models (Fig. 1-2), 2- highlight the marked increase in dose that occurs between maternal lifetime intake and the nursing infant (Fig. 3), and 3- demonstrate the effect of maternal dietary interventions at various ages on subsequent PCB-153 concentrations in human milk (Fig. 4-5).

Methods: The Haddad model is an 8-compartment physiologically-based pharmacokinetic (PBPK) model that has been validated by comparing estimated milk concentrations against concentrations measured in a Canadian Inuit population[1]. The Yang model is a 3-compartment PBPK model[2], and the EPA model is a single compartment, first-order kinetic model[3,4]. We compared the models by using data from 8 individuals who breastfed their infants for at least 11 months and represented a spread of average daily doses of the PCB congener 153 (PCB-153); data on these individuals, Canadian Inuits, were provided by Sami Haddad. Using the Haddad model, we also compared lifetime average maternal daily doses with average daily doses to infants during the nursing period (Fig. 3). Finally, using the EPA model, we calculated milk concentrations assuming dietary intervention, such as recognition and compliance with a fish advisory, at different life stages in the woman's life (Fig. 4-5).

Results: Simulated milk concentrations and doses to the infants from each of the 3 models for the selected individuals were similar within a factor of 2. EPA's model, the simplest, consistently calculated 1-year average milk concentrations that were the highest of the 3 models but still within a factor of 2 (See Figures 1-4) of the validated Haddad model. This suggests that the EPA model is accurate and protective and may be a good choice for risk assessors when evaluating lipophilic environmental contaminant concentrations in human milk . We found that PCB-153 doses to the infant were, on average 2 orders of magnitude higher than the maternal lifetime daily average (Fig. 3). Figures 4 and 5 depict the importance of early dietary intervention in a woman's life to prevent accumulation of PCB-153 that will later be passed on to the infant via nursing.



Methods

- All three models consider eating contaminated fish as the environmental exposure pathway.
- Simulations were run using all three models to calculate the concentration of PCB-153 in milk after 12 months of breast feeding (See Fig. 1).
- Simulations also calculated average daily dose to infants via nursing (See Fig. 2).
- All three models started using maternal average daily doses for 8 individual Inuit women.
- Maternal average daily doses were back-calculated from measured blood concentrations using the Haddad model.

Comparison of Models

Figure 1

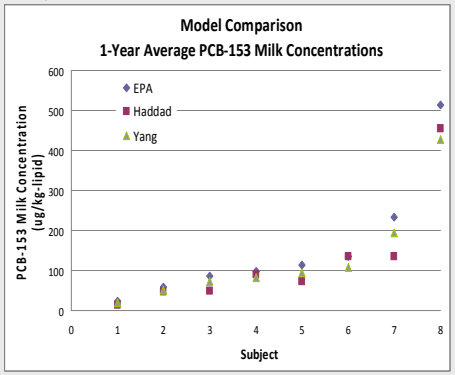
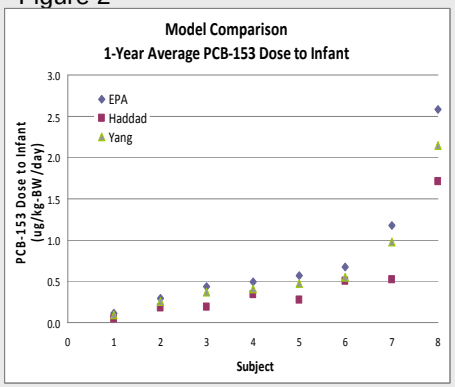


Figure 2



The three models produced simulated milk concentrations that were similar within a factor of 2. Milk concentrations simulated using the Haddad model correlate well with observed milk concentrations for the same individuals (R = 0.96, n = 75) [1]. Modeled doses to infants are also similar within a factor of 2. Milk concentrations and doses shown represent averaged values over the 12 month period.

Breastfeeding is still the healthiest food source for infants and none of the information presented here should be used to dissuade women from breastfeeding. The public health intervention suggested here is to further reduce the mother's exposure to environmental contaminants and to do so at an earlier age.

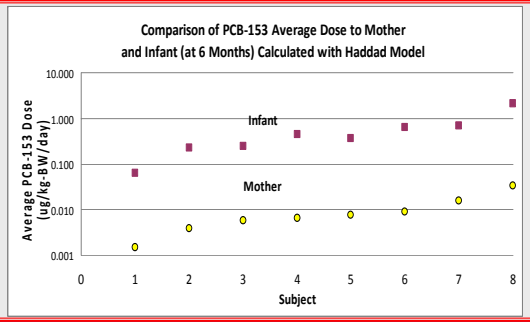


Figure 3. The infant's 6-month average daily dose of PCB-153 (through breastfeeding) is calculated to be 2 orders of magnitude higher than the mother's lifetime average daily dose regardless of the source of the mother's exposure and regardless of the magnitude of the mother's average daily dose.

Figure 4

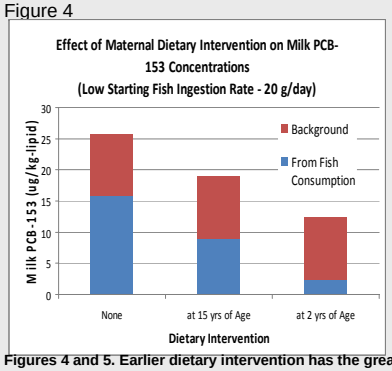
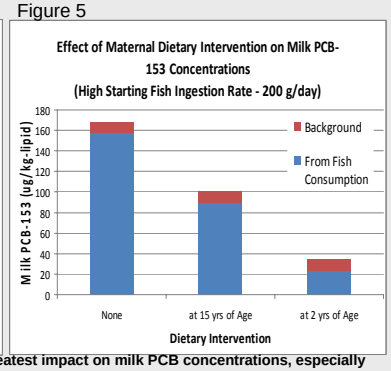


Figure 5



Figures 4 and 5. Earlier dietary intervention has the greatest impact on milk PCB concentrations, especially for high fish consuming populations. The background concentration (10 µg/kg-lipid) of PCB-153 in human milk was converted from the 2003-2004 NHANES [5] lipid-normalized serum data from people age 20-39 years using a partition coefficient of 1. Fish tissue concentration (0.0034 mg/kg-fish tissue) is hypothetical and was set to match the average oral lifetime daily doses of the 8 subjects in figures 1 and 2 at the arbitrary 200 g/day fish intake rate. A factor of 0.1 was applied to that dose for the 20 g/day fish intake rate.

Conclusions

- These 3 models compared favorably and suggest that the EPA model may be the simplest and sufficiently health-protective model for use in risk assessment.
- All 3 models suggest that the average daily dose of PCB-153 to the infant during the nursing period is approximately 2 orders of magnitude higher than the lifetime average daily dose to the mother.
- Models indicate that the earlier maternal exposure to PCB-153 is reduced, the greater the benefit to the nursing infant.

References

1. Verner, M.A., et al., *A physiologically based pharmacokinetic model for the assessment of infant exposure to persistent organic pollutants in epidemiologic studies.* Environ Health Perspect, 2009. **117**(3): p. 481-7.
2. Redding, L.E., et al., *Population physiologically-based pharmacokinetic modeling for the human lactational transfer of pcb 153 with consideration of worldwide human biomonitoring results.* Environmental Health Perspectives, 2008(11519): p. 1-29.
3. Smith, A.H., *Infant exposure assessment for breast milk dioxins and furans derived from waste incineration emissions.* Risk Anal, 1987. **7**(3): p. 347-53.
4. EPA, *Methodology for Assessing Health Risks Associated with Multiple Pathways of Exposure to Combustion Emissions.* 1998. (EPA 600/R-98/137).
5. Patterson, D.G., et al. *Levels in the U.S. Population of those Persistent Oreganic Pollutants (2003-2004) Included in the Tockholm Convention or in other Long-Range Transboundary Air Pollution Agreements.* Environ. Sci. Technol. 2009. **43**: p. 1211-1218 [Supplemental Information Tables S1-S6]